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In Vivo Evaluation of Modified Gum Karaya as a Carrier for Improving the Oral Bioavailability of a Poorly Water-Soluble Drug, Nimodipine

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ABSTRACT This work examines the influence of modified gum karaya (MGK) on the oral bioavailability of a poorly water-soluble drug, nimodipine (NM), in comparison with that of gum karaya (GK). A cogrinding method was selected to prepare mixtures of NM and GK or MGK in a 1:9 ratio (NM:GK/MGK). Differential scanning calorimetry (DSC), Fourier transmission infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), solubility studies, and in vitro release studies were performed to characterize the properties of the cogrinding mixtures. No drug-carrier interactions were found, as confirmed by DSC and FT-IR studies. The XRD study revealed that the crystallinity of NM was identical in both the cogrinding mixtures and was decreased when compared to that of physical mixtures or pure NM. The in vitro release rate of NM from both cogrinding mixtures was significantly higher than that of physical mixtures or pure NM. The in vivo study revealed that the bioavailability of NM from pure drug was significantly lower when compared to the cogrinding mixtures. The oral bioavailability was found to be NM powder < cogrinding mixtures of NM and GK < cogrinding mixtures of NM and MGK < NM solution. It can be inferred from the above results that MGK, an economical carrier, could be used for the dissolution enhancement of NM.

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INTRODUCTION

Gum karaya (GK), also called sterculia gum, is the dried exudation of the *Sterculia urens* tree and other species of *Sterculia*, which belong to the family Sterculiaceae [1]. GK is a negative colloid and a high-molecular-weight complex acidic polysaccharide. The general utility of GK is based on its viscosity [2]. It was successfully evaluated for its suitability in the preparation of hydrophilic matrices [3, 4], mini-matrices [5], microcapsules [6,7], and transdermal patches [8].

The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drugs is increasing [9, 10]. However, the high viscosity [11] and hardness [12] of these polymers limits their application as carriers in dissolution enhancement. Recently, our research group reported a modification to GK to provide a lower viscosity and showed its suitability as a disintegrant in tablet formulations [13]. This modified GK (MGK) was found to possess swelling comparable to that of the parent GK. Hence, it was evaluated as a carrier in the improvement of in vitro dissolution rate and efficiency of nimodipine (NM). NM is practically insoluble in water [14] and thereby exhibits low bioavailability after oral administration. To enhance

its bioavailability and therapeutic efficacy, NM's dissolution needed to be improved. Hence, NM was selected as a model drug: attempts were made to enhance its dissolution rate and efficiency by using MGK as the hydrophilic carrier [15]. MGK was found to significantly improve the dissolution rate of NM compared to GK in 1:9 wt/wt ratio (NM:GK/MGK), and the cogrinding technique was found to be an effective method for the preparation of the solid mixture [15]. The objective of the present investigation was to study the oral bioavailability of NM from its pure form and from cogrinding mixtures of NM and GK or MGK. The oral bioavailability of NM in solution was also estimated to determine the relative bioavailability of the cogrinding mixtures.

MATERIALS AND METHODS

Materials

NM and nitrendipine were gift samples from M/s USV Ltd (Bangalore, India) and M/s Sun Pharmaceuticals Industries Ltd (Mumbai, India), respectively. Girijan Co-operative Corporation Ltd (Visakhapatnam, India) supplied GK (Grade 1). All other materials used were of analytical reagent grade.

Methods

The MGK used in this study was prepared by the method reported by Murali Mohan Babu et al [13].

Briefly, powdered gum was placed in a porcelain bowl and subjected to heating using a sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling properties similar to GK's, but viscosity was decreased as a function of temperature and time period of heating. However, it was observed that GK samples were charred when heated at 140°C. In the preparation of MGK, no further change in viscosity of GK was observed by heating it at 120°C for more than 2 hours. Hence, these conditions of heating at 120°C for 2 hours were selected to prepare MGK. The prepared MGK was finally resieved (100 mesh) and stored in an airtight container at 25°C.

All experiments were carried out under light-protected conditions to prevent the photodecomposition of NM.

Preparation of cogrinding mixtures

Cogrinding mixtures of NM and GK or MGK were obtained by grinding a physical mixture of NM and GK or MGK in a 1:9 weight ratio [15] for 20 minutes in a ceramic mortar and sifted through 100 mesh. "CM-GK" is used to represent the cogrinding mixture of NM and GK, and "CM-MGK" is used to represent the cogrinding mixture of NM and MGK. To ascertain the effect of method, carrier, or both on the dissolution rate of NM, NM alone was ground for 20 minutes and the resultant product represented as NM_1. All the samples were stored in a desiccator at room temperature.

Physical mixture

The physical mixtures of NM and GK or MGK were obtained by simple blending of the NM and GK or MGK in a 1:9 wt/wt ratio (drug:polymer) with a spatula. PM-GK and PM-MGK are used to represent the physical mixtures of NM-GK and NM-MGK, respectively.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) curves were obtained by a differential scanning calorimeter (DSC 220C, Seiko, Tokyo, Japan) at a heating rate of 10°C/min from 30 to 300°C in a nitrogen atmosphere.

X-ray Diffraction studies

Powder X-ray diffraction (XRD) patterns were recorded using a Philips diffractometer (PW 1140, Philips, Osaka, Japan) and Cu-ka radiation. Diffractograms were run at a scanning speed of 2°/min and a chart speed of 2°/2 cm/2Θ.

Infrared spectroscopic studies

Fourier–transformed infrared (FT–IR) spectra were obtained on a PerkinElmer 2000 FT–IR system (PerkinElmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Solubility studies

The apparent solubility of NM, NM_1, cogrinding mixtures, and physical mixtures was determined in water at 37°C. For each preparation, an equivalent of 50 mg of drug was added to 50 mL of water in a conical flask with Teflon-lined screw caps. The conical flasks were kept on a shaker incubator maintained at 37 ± 0.5°C for 24 hours. After shaking, the flasks were kept equilibrated in an incubator at 37 ± 0.5°C for 12 hours. Then solution was filtered through a 0.45-µm Millipore filter and the filtrate was assayed spectrophotometrically at 240 nm.

In vitro dissolution rate studies

Dissolution rates from different solid mixtures were determined in 900 mL of distilled water (pH 5.5-6) containing 0.2% wt/vol sodium lauryl sulfate at 37°C with a stirrer rotation speed of 50 rpm using the USP XXI dissolution rate test apparatus employing a paddle stirrer (Method II). A 5-mL aliquot of dissolution medium was withdrawn at 5, 10, 20, 30, 45, 60, 90 and 120 min with a pipette having a prefilter (membrane filter, 0.45 µm). The samples were suitably diluted and assayed spectrophotometrically at 240 nm. Each dissolution rate test was repeated 3 times.

As a model-independent approach, dissolution efficiency (DE), as suggested by Khan, was employed to evaluate the dissolution rate of NM from different solid mixtures [16]. DE is defined as the area under the dissolution curve up to the time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. DE_{10} and DE_{30} values were calculated from the dissolution data and used for comparison.

Bioavailability studies

A 4-subject Latin square crossover design was applied to carry out the study to avoid variations caused by time and animals. Four male rabbits weighing 2.0 to 2.5 kg were fasted overnight; water was allowed ad libitum. A dose equivalent to 5 mg of NM per kg of body weight of rabbit was given in a hard gelatin capsule (no. 3). In the case of NM solution (NM was dissolved in a minimum quantity of 95% vol/vol ethanol), the solution was given to the rabbits with the help of oral tubing. Blood samples were taken at 0 (before drug administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 7, and 8 hours after administration of the drug. Water only, not food, was provided during the trial. A washout period of 7 days was allowed between the first, second, third, and fourth trials in individual subjects.

The drug concentration in plasma was analyzed by a modified high-performance liquid chromatography (HPLC) method [17]. The chromatographic system consisted of a Model 2800 Bio Rad Solvent Delivery System, a reversed phase Bio Sil ODS-55 (catalog 125-0080, 250 mm x 4 mm) column, and a detector (Bio Rad UV monitor model 1306) operating at 238 nm (Biorad, California, US). The mobile phase consisted of water:acetonitrile:methanol (37.5:37.5:25 vol/vol) at a flow rate of 1 mL/min. A guard column (Bio Rad Model 1250131) was used.

To 500 µL of plasma sample, 100 µL of internal standard (nitrendipine, 1 µg/mL) solution was added into a microcentrifuge tube. Ethyl acetate (1 mL) was added to each tube, which was then shaken on a horizontal shaker for 30 minutes, followed by centrifugation (Model No. C 4S, Kadavil Electro Mechanical Industries, Perumbavoor, India) at 5000 rpm for 20 minutes. Then, the organic layer was transferred to a clean microcentrifuge tube and evaporated to dryness under nitrogen gas in a water bath at 40 to 50°C. The resultant residue was reconstituted with 200 µL of mobile phase, and a 20 mL aliquot was injected into the HPLC system.

The limit of quantification for NM was 10 ng/mL of plasma. At this concentration the accuracy was 96.4% while the precision was 10.7%. During the

validation within-batch accuracy ranged from 94.5% to 103.8%, while within-batch precision remained below 14.2%. The between-batch accuracy ranged between 96.7% and 105.1%, while precision remained below 11.2%.

Data analysis

Data were generated assuming first-order absorption and 1 compartment model with first-order elimination. The maximum plasma concentration (C_{max}) and time of its occurrence (T_{max}) were directly computed from the plasma concentration vs time plot. The elimination rate constant (K_{el}) was determined from the terminal phase of the log plasma concentration vs time profile by least squares regression analysis. From this, K_{el} was calculated as $K_{el} = 2.303 \times$ slope. The elimination half-life ($t_{1/2}$) was calculated using the formula $t = 0.693/K_{el}$. The area under the curve from 0 to 8 hours (AUC_{0-8}) is calculated using the trapezoidal rule. The absorption rate constant (k_a) was calculated using the Wagner-Nelson method [18]. Relative bioavailability was calculated with reference to oral solution:

$$\% \text{ relative bioavailability of test product (F)} = \frac{AUC_{0-8} \text{ test product}}{AUC_{0-8} \text{ oral solution}} \times 100$$

The solubility data, DE values, and pharmacokinetic parameters of the formulations were statistically evaluated using analysis of variance (ANOVA). In the case of normal distributed results, equal variance test was used, while Kruskal-Wallis 1-way ANOVA was used for nonnormal distributed data. All tests were performed at a level of significance of $P < .001$ for DE values and $P < .05$ for pharmacokinetic parameters. Results are expressed as the mean ± standard deviation.

RESULTS AND DISCUSSION

Solid-state studies

The DSC thermograms of NM, NM_1, GK, and MGK are compared with those for cogrinding mixtures and physical mixtures in Figure 1. The DSC thermograms of physical mixtures as well as cogrinding mixtures showed 2 peaks corresponding to the melting of 2 polymorphs of pure NM, indicating the absence of a well-defined chemical interaction between NM and GK or MGK. NM_1 (ground NM) also exhibited 2 endothermic peaks at 114 and 125.5°C, similar to NM, as observed in our previous study [15]. The decrease in sharpness and intensity of endothermic peaks observed with the cogrinding mixtures could be attributed to the conversion of most of the crystalline form of the drug to the amorphous form.

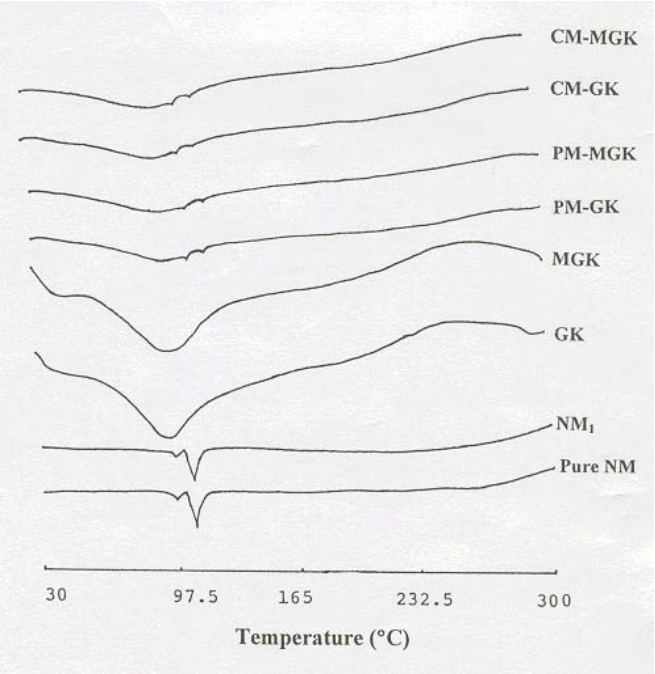

Figure 1. Endothermic behavior of physical mixtures and cogrinding mixtures of NM and GK or MGK (1:9) in comparison with pure NM, NM_1, GK, and MGK.

The FT-IR spectra of NM, physical mixtures, and cogrinding mixtures are shown in Figure 2. Physical mixtures and cogrinding mixtures of NM with GK or MGK were also found to be identical. The principal IR absorption peaks of NM at 3331 cm^{-1} (-NH-stretching), 3102 cm^{-1} (CH-stretching), 2933 cm^{-1} (CH-aliphatic), 1693 cm^{-1} (C=O-ester), 1621 cm^{-1} (C=C-aromatic), 1522 cm^{-1} ($-NO_2$,), 1381 cm^{-1} (-C-CH3), and 1133 cm^{-1} (-C-O-ester) were all observed in the spectra of NM and solid mixtures with MGK or GK. This spectral observation also thus

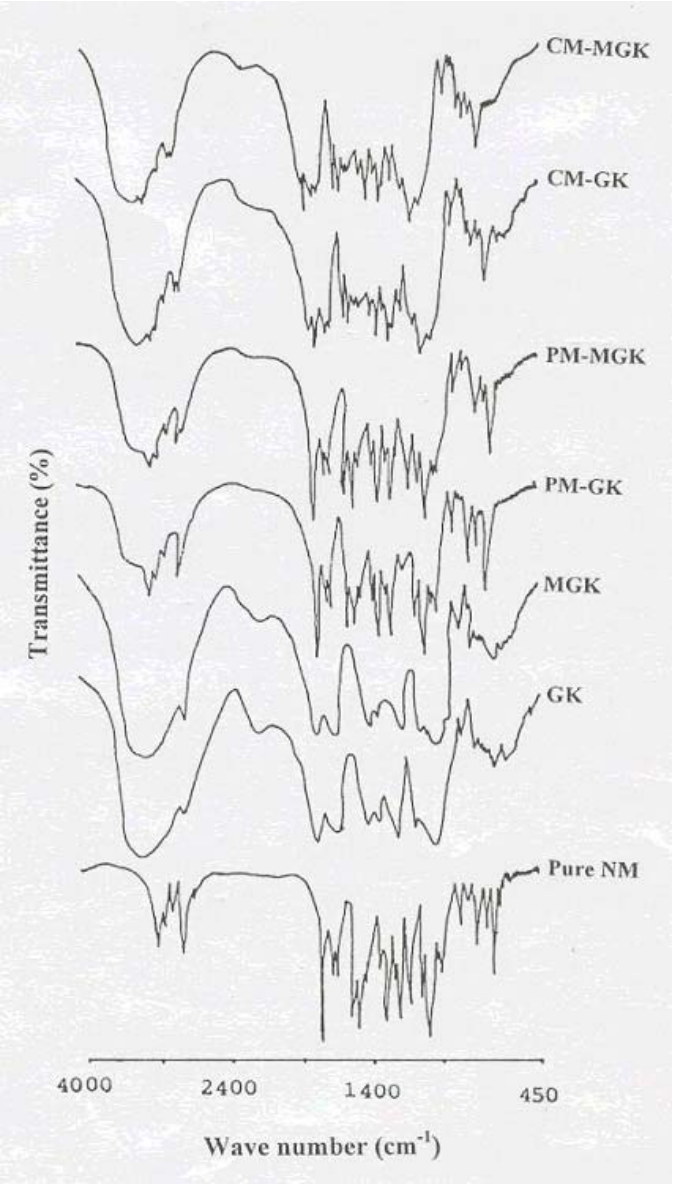

Figure 2. FT-IR spectra of physical mixtures and cogrinding mixtures of NM and GK or MGK (1:9) in comparison with pure NM, GK, and MGK.

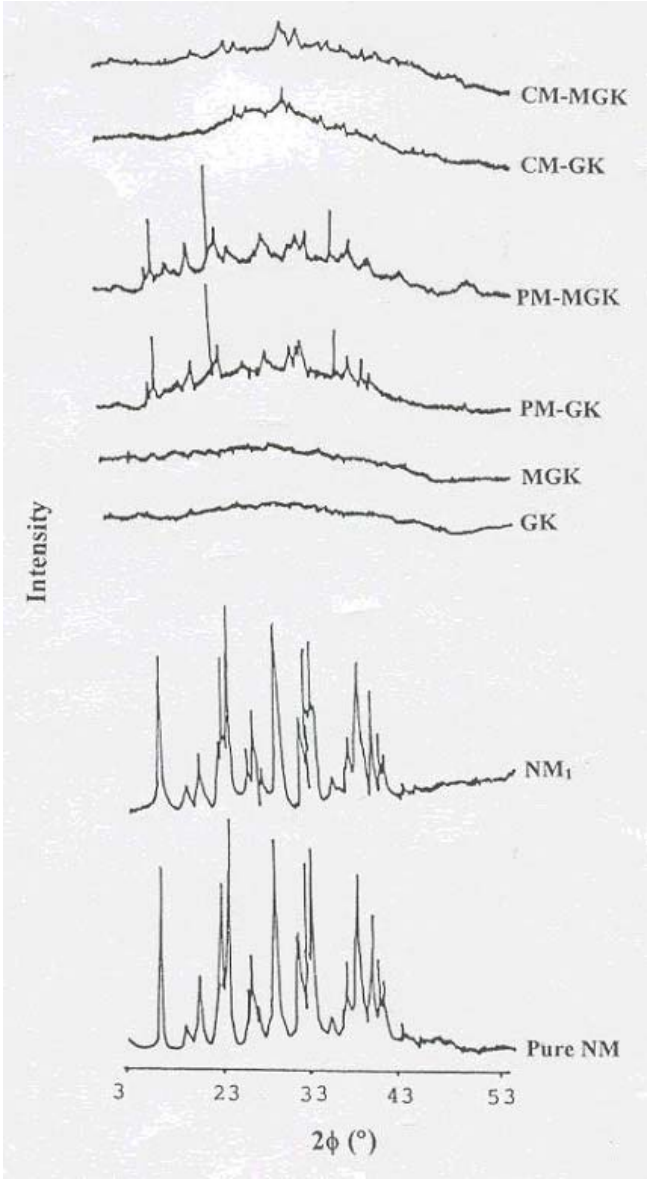

Figure 3. XRD patterns of physical mixtures and cogrinding mixtures of NM and GK or MGK (1:9) in comparison with pure NM, NM_1, GK, and MGK.

indicated no interaction between the NM and MGK or GK.

The XRD patterns of NM, NM_1, GK, and MGK are compared with those of cogrinding mixtures and physical mixtures in Figure 3. Both the physical mixtures possessed the diffraction peaks of NM crystals, indicating that NM was in the crystalline state. Though the NM was ground for 20 minutes (NM_1), NM_1 showed all the peaks shown by pure NM. It was also observed that the intensities of the peaks showed by NM_1 were higher than those of physical mixtures. The reduction in the intensity of the sharp peaks and the broadening of some peaks of NM in both cogrinding mixtures suggested that a small portion of NM existed in the microcrystalline form. This indicated that NM was partially converted to an amorphous form. This finding is compatible with the enhanced dissolution rate of NM from CM-GK and CM-MGK.

Solubility studies

Solubility data for NM, NM1, PM-GK, PM-MGK, CM-GK, and CM-MGK are given in Table 1. Though the solubility of NM from cogrinding mixtures increased, the solubility of NM from either of the physical mixtures not increased significantly. ANOVA ($P < .001$) performed on the solubility parameter demonstrated that there was a statistically significant difference between the solubility of NM from cogrinding mixtures with that of NM_1. As observed in the previous studies [15], it was also found that there was no statistically significant difference between the solubility of CM-GK and CM-MGK, indicating that GK and MGK have a similar effect on improving the solubility of NM. The solubility of NM_1 did not differ significantly from that of pure NM, indicating that the grinding of the pure NM did not change the solubility characteristics of NM.

In vitro release studies

Figure 4 shows the in vitro dissolution profiles of the physical mixtures and the cogrinding mixtures in comparison with pure NM and NM1. The values of DE_{10} and DE_{30} are given in Table 1. NM_1 exhibited a dissolution profile similar to that of pure NM, as indicated by the DE values. It is evident that the rate of dissolution of NM and NM_1 is very low compared with those of all mixtures tested. Both the physical mixtures had slightly improved dissolution patterns compared with the NM powder. PM-MGK, however, showed more improvement in NM dissolution, when compared with PM-GK. Though the NM dissolution from CM-GK also improved, the increase in dissolution rate of NM from CM-MGK was found to be greater. ANOVA ($P < 0.001$) performed on the parameters DE_{10} and DE_{30} demonstrated that the differences were statistically significant. The rank order according to DE values is NM/NM_1 < PM-GK < PM-MGK < CM-GK < CM-MGK. These results confirmed that the improvement in dissolution rate of NM was due to the presence of GK or MGK, and not due to the decrease in particle size of NM during grinding.

Table 1. Solubility and DE Values (Mean ± Standard Deviation) of NM from Pure NM, Ground NM, Physical Mixtures, and Cogrinding Mixtures (n = 3)

Product	Solubility (µg/mL)	DE_{10}	DE_{30}
NM	2.78 ± 0.4	4.95 ± 0.390	9.03 ± 0.926
NM_1	2.79 ± 0.6	5.01 ± 0.430	9.36 ± 0.990
PM-GK	3.42 ± 0.4	6.75 ± 0.906	11.80 ± 1.275
PM-MGK	3.51 ± 0.6	10.82 ± 1.196	16.17 ± 1.417
CM-GK	11.91 ± 1.7	22.52 ± 0.776	38.84 ± 1.580
CM-MGK	12.23 ± 1.2	49.37 ± 2.118	74.75 ± 1.871

Cogrinding of NM with GK or MGK resulted in transformation of large crystals of NM to smaller crystals, as indicated by XRD studies, leading to increased surface area available for dissolution. Moreover, the hydrodynamic microenvironment around the particles was changed because of the hydrophilic nature of the carrier [19]. From the results obtained, it appears decreased crystallinity resulting in increased solubility of drug particles contributed to the improvement of dissolution rate of NM from the cogrinding mixtures. The slight increase in the dissolution rate of NM from physical mixtures as compared with the pure drug is likely due to the ability of the polymer to enhance the wettability of the hydrophobic NM particles.

The results of dissolution studies also revealed the importance of the viscosity of the hydrophilic polymer. During the process of drug dissolution from ordered mixtures of drug and the hydrophilic carrier, when a drug-carrier particle comes in contact with the dissolution fluid, seeping of dissolution medium into the drug-carrier particle takes place, which initiates the formation of a stagnant gel layer of carrier around the particle. Therefore, the diffusion of dissolved drug through the gel layer is a determining factor in the enhancement of dissolution rate. The higher the viscosity of the carrier, the greater the diffusion barrier formed around the drug particle. It was also evidenced from the Stokes-Einstein equation that the diffusion coefficient is inversely proportional to viscosity. Hence, as the carrier concentration is increased, the dissolution rate of the drug decreases [20]. The viscosity of 1% wt/vol solution of MGK at 28°C is 550 cps, which is about 3 times lower than that of GK [15]. Hence,

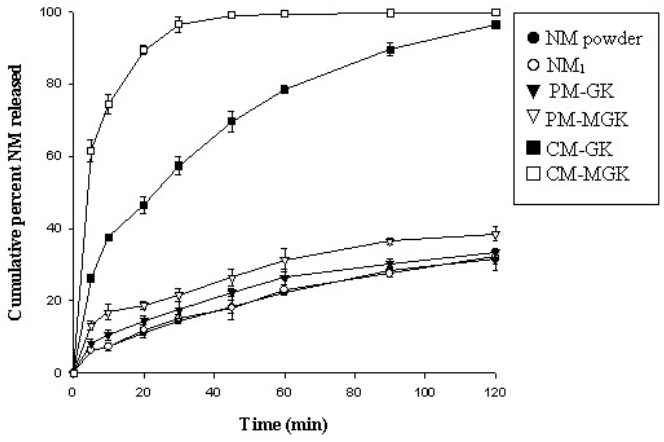

Figure 4. Dissolution profiles of NM from physical mixtures and cogrinding mixtures of NM and GK or MGK (1:9) in comparison with NM powder and ground NM (NM_1).

the dissolution rate of NM is low from physical/cogrinding mixtures containing GK, though the physical state of the drug is identical in the physical/cogrinding mixtures of GK with respect to mixtures of MGK. During the dissolution process, the drug particles that are not agglomerated but disperse rapidly throughout the dissolution medium expose a greater surface area, resulting in rapid drug release. It was observed that GK, which is more viscous than MGK, resulted in the formation of lumps of drug-carrier particles during dissolution, whereas NM-MGK particles dispersed rapidly. This factor also contributed to the significant difference between the dissolution rates of CM-GK and CM-MGK.

In vivo evaluation

An animal study was carried out to determine the absorption behavior of NM from the 4 NM preparations (CM-GK, CM-MGK, NM powder incorporated in capsules, and NM solution), which were administered orally to rabbits. Figure 5, shows the plasma drug concentrations as a function of time after oral administration of these preparations; the NM pharmacokinetic parameters such as C_{max}, T_{max}, $t_{1/2}$, K_a, AUC_{0-8}, and F are summarized in Table 2. A statistical summary of all the results obtained by subjecting the pharmacokinetic data to ANOVA is given in Table 3.

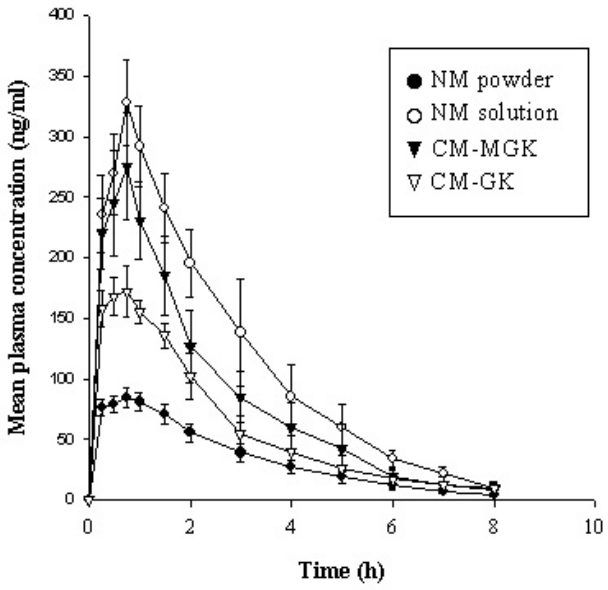

Figure 5. Mean plasma concentration-time profiles of NM after oral administration of NM solution, NM powder and co-grinding mixtures of NM and GK or MGK at a dose 5 mg kg–1 to rabbits. Each data point represents the mean ± standard deviation.

Peak plasma concentration (T_{max}) of NM was obtained at 0.75 ± 0.20 hours for all the products, as shown in Table 2. There was no significant difference between T_{max} values for all the products. Peak plasma concentration (C_{max}) values of 82.73 ± 10.26, 316.93 ± 49.12, 259.10 ± 63.92, and 181.54 ± 10.58 ng/mL were observed after oral administra

tion of NM powder, NM solution, CM-MGK, and CM-GK, respectively (Table 2). These results revealed that the NM solution gave the highest C_{max} value, followed by CM-MGK. However, there was no significant difference between C_{max} values of CM-MGK and NM solution. A significant difference was observed in CM-GK and NM solution. It was also found that there was no significant difference between the C_{max} value of NM powder and CM-GK.

The $t_{1/2}$ values for NM were found to be 1.64 ± 0.073, 1.45 ± 0.16, 1.44 ± 0.14, and 1.66 ± 0.39 hours after administration of NM powder, NM solution, CM-MGK, and CM-GK solid mixtures, respectively. The statistical data regarding $t_{1/2}$ given

Table 2. Pharmacokinetic Parameters (Mean ± Standard Deviation) of NM Following Oral Administration of NM Powder, NM Solution, and Cogrinding Mixtures of NM and Carrier (GK or MGK) (1:9) to Rabbits (n = 4)

Parameter	NM Powder	NM Solution	CM-MGK	CM-GK
C_{max} (ng/mL)	82.73 ± 10.26	316.93 ± 49.12	259.10 ± 63.92	181.54 ± 10.58
T_{max} (hr)	0.75 ± 0.20	0.75 ± 0.20	0.75 ± 0.20	0.75 ± 0.20
$t_{1/2}$ (hr)	1.64 ± 0.073	1.45 ± 0.16	1.44 ± 0.14	1.66 ± 0.39
K_a (hr^{-1})	0.53 ± 0.007	1.09 ± 0.42	0.73 ± 0.13	0.59 ± 0.06
AUC_{0-8} (ng/hr/mL)	272.13 ± 38.95	930.48 ± 139.92	678.19 ± 158.65	487.46 ± 75.98
F (%)	29.30 ± 1.59	100 ± 0.00	72.76 ± 12.60	52.42 ± 3.28

Table 3. Statistical Summary of Pharmacokinetic Parameters (P < .05)*

Parameter	C_{max}†	T_{max}†	K_a†	AUC_{0-8}†	$t_{1/2}$‡	F†
NM powder vs NM solution	S	NS	S	S	NS	S
NM powder vs CM-MGK	S	NS	S	S	NS	S
NM powder vs CM-GK	S	NS	NS	S	NS	S
NM solution vs CM-MGK	NS	NS	S	S	NS	S
NM solution vs CM-GK	S	NS	S	S	NS	S
CM-MGK vs CM-GK	S	NS	S	S	NS	S

* NS indicates nonsignificant; S, significant.

†Kruskal-Wallis 1-way ANOVA on ranks.

‡Equal variance test.

in Table 3 indicated that there is no significant difference between these values.

Application of the Wagner-Nelson method to the plasma concentration data indicated that maximum absorption was obtained for all products at 0.75 hours. The Ka values (Table 2) were found to be 0.53 ± 0.007, 1.09 ± 0.42, 0.73 ± 0.13, and 0.59 ± 0.06 hr^{-1} for NM powder, NM solution, CM-MGK, and CM-GK, respectively. These results indicated that the rate of absorption of NM from NM solution and CM-MGK was faster compared to that for NM powder and CM-GK. These results thus supported the in vitro dissolution data, where the dissolution was significantly increased in CM-MGK compared to CM-GK and NM powder.

The AUC_{0-8} values for the NM powder, NM solution, CM-MGK, and CM-GK cogrinding mixtures were found to be 272.13 ± 38.95, 930.48 ± 139.92, 678.19 ± 158.65, and 487.46 ± 75.98 ng/hr/mL^{-1}, respectively. The order of preparations according to their oral bioavailability is NM solution > CM-MGK > CM-GK > NM powder. The relative bioavailability (F) of NM from NM powder, CM-MGK, and CM-GK was found to be 29.30% ± 1.59%, 72.76% ± 12.60%, and 52.42% ± 3.28%, respectively. These values clearly indicated the improvement in bioavailability of NM from cogrinding mixtures when compared to the powder dose of NM, confirming that an increase in solubility and dissolution rate enhances oral bioavailability. When compared to CM-MGK, CM-GK bioavailability is significantly less, though both products contain NM in a similar form, as evidenced from DSC and XRD studies. In vitro dissolution studies also gave similar results, confirming that the viscosity of GK might be the influencing factor in the low bioavailability of NM from the NM-GK cogrinding mixture.

These results indicate that the bioavailability of NM was improved significantly when administered as a cogrinding mixture with MGK. The results clearly revealed that the viscosity of the carrier used in cogrinding mixtures influenced the oral bioavailability of the poorly water-soluble drug NM. The lower the viscosity of the carrier used, higher the bioavailability of the poorly soluble drug, provided the carriers having comparable swelling capacity. From the above results, it was obvious that the cogrinding mixture with MGK could be useful in developing a dosage form with improved dissolution rate and oral bioavailability of poorly water-soluble drugs.

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